REMARKS

While the status of claims 8-11 is withdrawn, it is respectfully submitted that the Examiner will recognize that there is a allowable generic or linking claim and it is respectfully requested that these claims be examined.

In the parent application, a rejection was advanced under 35 U.S.C. § 103 based on Schafer in view of Tosa and Carter or over Schafer in view of Tosa and Sutherland. It is respectfully submitted that these rejections should not be applied to the claims as amended herein.

The present invention relates to assays which are conducted such that a component, for instance a labeled ligand, becomes at least partially bound to a solid body which can be, for instance, an optical waveguide. As a result of the binding, there is a change in an analyte dependent parameter, for example, a fluorescence emission which is associated with the labeled ligand, which can then be measured.

In the prior art methods, such assays are calibrated using known concentrations of ligands and standard curves. An unknown concentration of ligand can subsequently be determined using the standard curves and in such prior art methods, the unknown concentration of the ligand is determined only once.

The Applicants recognized that during the course of these assays, a reliable measurement of the bound or absorbed component, i.e., without interference from the free components in the assay system, can be obtained by direct continuous monitoring of the component. Thus, an important aspect of the current invention is that, in contrast to the prior art, an unknown sample is determined continuously. The advantages of such a method are described, *inter alia*, on page 4, lines 6-17. One of the advantages of the invention is that there is an ability to obtain an indication of the

unknown concentration of ligand at an early stage in the assay and the ability to spot and avoid random errors.

The primary reference relied heretofore, Schafer, is concerned with overcoming the problems which are inherent in "Heidelberger" non-monotonous calibration curves. See col. 1, line 62 et seq. There is no direct correlation in such curves between the concentration of analyte and the measured parameter, e.g., absorbance. Figures 1 and 2 of Schafer illustrate the problem. In Figure 1, it can be seen that there is no direct correlation between concentration and absorbance of a particular sample after 300 seconds (note the curves for concentration C1 and C3 cross). When the same data is plotted in the form of concentration C against a measure of the absorbance X (Figure 2), a hook-shaped "Heidelberger" curve is obtained. As apparent, an unknown sample which has an absorbance X might have one or two different concentrations, one of which falls in the part of the curve labeled "A" and the other falls in the part of the curve labeled "B". For instance, it can be seen that an unknown sample with an absorbance X of 0.8 might have a concentration of either 0.5 or 4.

Schafer provides an answer to this problem by providing a multi-step process. First, a number of "training runs" are carried out in which a property associated with the sample, S(t), is plotted against time for a number of different concentrations. S can be, for instance, absorbance of the sample or a valued derived from the absorbance of the sample, for example, the difference between absorbance after 12 seconds and 300 seconds (see example 1, col. 11, lines 18-20). This is, in essence, a calibration step shown by Figure 1. It can be loosely said that the data is apparently measured in a "continuous" manner but, as apparent from col. 7, lines 23-26, the data is not measured "continuously" but rather is measured at discrete time points.

In the next step, at least one set of data ("discriminators") is derived from a graph of it. The data or discriminators are merely variables based on physical properties of the sample such as its absorbance, slope of the graph at a particular point, curvature of the graph, and the like. In example 1 (col. 11, line 39), the discriminator chosen are five gradients of the graph, taken at the time points t1/t2, t2/t3, t3/t4, t4/t5, and t5/t6 and the fifth absorbance value. These data points are contiguous and they might therefore be said to represent continuous data that has been derived or manipulated from the analyte dependent parameter.

A statistical algorithm is derived which uses the discriminators as variables. "Scores" are given to each of the concentrations of the standard samples on the basis of whether or not the concentrations fall in part A or part B of the "Heidelberger" curve (Figure 2). A "boundary score" is determined at dividing the scores whose concentration fall into part A of the curve from those which fall into part B of the curve.

The foregoing steps are repeated in order to refine the algorithm (the "operative discrimination algorithm") which describes the relationship between concentrations of the standard samples and the discriminators. In example 1, the algorithm makes use of 5 contiguous gradients. This completes the calibration of the assay.

In an analysis, an unknown sample is tested. First, a graph of absorbance or some other physical property of the sample against time is plotted for the sample of unknown concentration in the same manner as the calibration process. Using the "operative discrimination algorithm" from the calibration, an "analysis score" is given to the unknown sample. However, it will be appreciated that the "analysis score" itself is a single value which is derived from the graph of the unknown sample even though

the "operative discrimination algorithm" that is used to obtain the "analysis score" might use data from contiguous time points.

Next, the "analysis score" is compared to the "boundary score" to determine whether the "analysis score" falls into part A or part B of the curve. The concentration of the unknown samples is thus determined from knowledge of its absorbance and the calibration curves and information from the determination.

It will be appreciated from the foregoing that the concentration of the unknown sample is obtained in a relatively standard manner, merely by reading off the concentration value that corresponds the physical property X from the standard curves. The only "continuous" data which arguably derived from the initial data is that which is used in the "operative discrimination algorithm", which used to determine whether the concentration value obtained from the standard graph falls within part A or part B of the curve. Thus, any derived "continuous" data does not itself "determine an unknown sample" but rather is used only to assist in distinguishing between one of two possible values which the single determination of the unknown sample can take. In the claimed invention, the unknown sample is determined continuously.

In the last Office action, the Examiner cited a passage from Schafer which starts at column 9, line 63. This passage relates to the "analysis run" i.e., the determination of the concentration of the unknown sample. It essentially states that a property of the unknown sample ((S)t) is tested against time in the same way as the calibration samples were tested. The "operative discrimination algorithm" is then applied to the data provided in the graph and then "**an** analysis score is calculated from [the data from the graph] . . . ." (emphasis added) This passage does not disclose the continuous quantitative determination of an unknown sample.

Schafer's method is primarily concerned with distinguishing the results obtained from assays that produce "Heidelberger curves". It is not concerned with obtaining results from assays which have not yet reached equilibrium. Note that at col. 6, lines 30-33, Schafer notes that it is common practice to use as the input variable an "end point or plateau value". Another reference to this plateau value is found in the last paragraph in column 5. This teaches that Schafer's method relates to the measurement of an end point value, an equilibrium value from which the concentration of the unknown sample is determined. In the claimed invention, there is continuous determination before equilibrium is established.

The Tosa reference was relied on in the previous Office Action for the purpose of disclosing an assay involving an immunochemical binding reaction on a waveguide surface in order to enable to monitoring of a reaction by luminescence detection. Such a teaching does not cure the basic deficiencies in Schafer vis-à-vis the claimed invention. In addition, there is no motivation for combining Tosa with Schafer for reasons discussed in detail in an earlier response.

The Carter reference was cited as an example of providing a waveguide surface for specific binding assays as providing evidence that the heterogeneous technique was well know for providing a number of advantages. It is not seen where this additional reference adds anything further to the disclosure of Tosa but, in fact, it is submitted that this shows there was a lack of motivation. If the use of heterogeneous assay such as those described in Carter (1986) were an obvious substitution, then Schafer (filed in 1993) would have either made the substitution or suggested the assays described were also applicable to heterogeneous assays.

Southerland does not cure any of the deficiencies in the basic combination of references. It relates to the use of an optical waveguide for optically ascertained

parameters of the species in liquid analyte. It, like Tosa, always uses steady state measurements to establish a relationship between those values.

In light of all of the foregoing considerations, it is respectfully submitted that the Examiner will recognize on further consideration that the claims of this application satisfy the requirements of 35 U.S.C. § 103.

The early examination and allowance of this application are respectfully solicited.

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Respectfully submitted,

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